GENES THAT MARK AND MEDIATE BREAST CANCER METASTASIS TO LUNG

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Metastasis, or the malignant spread of cancer from its primary site of tumorigenesis to a distant organ, is the most deadly consequence of breast cancer. In spite of numerous advances in the clinical management of this disease, current treatment regimens enable only a 10-month median survival for breast cancer patients that suffer from malignant spread to the lungs, liver, or brain. Understanding the mechanisms that mediate this metastatic process is pivotal for the development of novel therapeutic modalities that may improve the survival of patients with this deadly condition.

To identify genes that may be mediators of breast cancer metastasis to the lung, we xenografted a heterogeneous population of MDA-MB-231 human breast cancer cells intravenously into immunocompromised mice. Taking advantage of the mouse as a "cell-sorter" for highly metastatic cells, we isolated first and second generation subpopulations of breast cancer cells that were extracted from lung metastatic lesions, which exhibited successively enhanced lung metastatic activity. The parental cell line, as well as its highly metastatic progeny, were transcriptomically queried using Affymetrix oligonucleotide microarray technology, and class comparisons identified a 95-gene expression signature that correlated with lung metastatic behavior. This signature was tissue-specific, as it was largely distinct from a previously identified bone metastasis signature for the same cell line. Furthermore, overexpression and knockdown strategies identified at least 8 of these genes as being causally involved in the lung metastatic process.

To assess the clinical relevance of these findings, an Affymetrix gene expression dataset of 82 untreated primary breast cancers that were surgically extracted at the Memorial Sloan-Kettering Cancer Center and had at least three years of clinical follow-up was queried for expression of the lung metastasis signature. Clustering analysis and class prediction algorithms revealed that patients harboring tumors that expressed the lung metastasis signature were more likely to develop distant recurrence to the lung during the clinical progression of the disease. This approach allowed us to identify a subset of genes from the lung metastasis signature that confer metastagenicity functions—selected for in the primary tumor, and coincidentally enable basal growth/metastatic ability in the lung microenvironment. Consistently, MDA-MB-231 cells that overexpress these lung metastagenicity genes have a growth advantage when implanted into the mammary fatpad, and have enhanced lung metastatic activity when injected intravenously.

Thus, we have identified genes that correlate with and mediate breast cancer metastasis to lung. In addition, preliminary data supports a predictive role for these genes in identifying primary breast cancers that have an increased likelihood of developing lung metastasis. Additional work will be necessary to establish the utility and efficacy of these genes both as prognostic markers and as targets for metastasis therapy.

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